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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,653	01/17/2002	David Henry Small	009621-39189	8742

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GIBBONS, DEL DEO, DOLAN, GRIFFINGER & VECCHIONE
1 RIVERFRONT PLAZA
NEWARK, NJ 07102-5497

EXAMINER	
KOLKER, DANIEL E	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/051,653	SMALL ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) *5-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *1-8* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 7/16/02, 7/22/02, 8/26/02
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 – 8 are pending in the instant office action.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1 – 4, in the reply filed on 30 November 2004 is acknowledged.

Claims 5 – 8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 30 November 2004.

Claims 1 – 4 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 – 3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for diagnosis of Alzheimer's disease, does not reasonably provide enablement for the diagnosis of any other condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to methods of diagnosing disorders associated with altered protein glycosylation. The specification discloses a method of diagnosing Alzheimer's disease, and contemplates the use of said method in the diagnosis of prion disorders (see p. 2, final sentence). However, Pergami et al. (1996. Analytical Biochemistry 236:63-73) teach that both the infectious and non-infectious forms of the prion protein bind equally well to wheat germ agglutinin (WGA) immobilized on a solid support (see p. 72, first column, second complete paragraph). Therefore the skilled artisan could not use a WGA-based method in the detection of prion diseases. Furthermore the specification discloses (p. 6, lines 6 – 9) that Parkinson's disease and multiple sclerosis do not show alterations in levels of WGA-reactive glycoproteins. Therefore the method could not be used in the diagnosis of those diseases. In fact, there are numerous diseases that are associated with altered protein glycosyation. For example, Dennis

(U.S. Patent 5,427,914, issued 27 June 1995) teaches that lectin binding is correlated with tissue invasiveness of specific tumors (see paragraph that spans columns 1 and 2). Malignant tumors are disorders associated with altered protein glycosylation, but a skilled artisan would not use the instant method to determine whether or not a tumor is invasive, as there is no *a priori* reason to believe that wheat germ agglutinin would in fact be able to distinguish between specific tumors.

Bies et al. (2004. Advanced Drug Delivery Reviews 56:425-435) teach that "different cell types express different glycan arrays" (p. 426, second column) and that lectins recognize sugars attached to proteins with a very high degree of specificity (p. 426, first paragraph). Therefore, in order for the claimed method to be practiced with any disorder associated with altered prtotein glycosylation, one would have to first conduct a series of experiments to determine if the disorder were in fact associated with alterations in WGA affinity.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988). The nature of the invention, diagnosis of diseases based on changes in the sugar molecules attached to proteins, is complex. The claims are drawn to the diagnosis of any disorder that is associated with any alteration in glycosylation pattern of any protein, even if said protein is not contained in an appropriate body fluid. The prior art teaches that the level of predictability is low; i.e. lectins recognize specific patterns of sugar molecules which vary greatly across proteins and disease state. The specification does not provide any working examples for diagnosing diseases other than Alzheimer's disease, and furthermore the prior art teaches that WGA is not able to distinguish between normal and pathogenic forms of prion protein. Therefore, an undue amount of experimentation would be required to practice the method commensurate in scope with the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 – 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saez-Valero et al. (reference AJ on the information disclosure statement filed 26 August 2002) in view of Sigma Chemical Catalog 1994 and Savage et al (1992. Avidin-Biotin Chemistry: A Handbook. Rockford, Illinois: Pierce Chemical Company). The claims are drawn to methods of diagnosing disorders or Alzheimer's disease by mixing proteins from samples with labeled WGA. Saez-Valero et al. teach a method of diagnosing Alzheimer's disease (AD) by combining samples of protein isolated from cerebrospinal fluid (CSF) with WGA and analyzing the different glycosylation patterns in proteins from AD and non-AD patients. See specifically Experimental Procedures, p. 1601 – 1602. The method of Saez-Valero et al. includes the following steps:

1) Isolate protein from CSF of Alzheimer's and non-Alzheimer's patients
2) Mix protein with WGA or Con A immobilized on sepharose
3) Separate bound protein from free protein
4) Detect amount of acetylcholinesterase (AChe) in unbound fraction
5) Calculate ratio of AChe in unbound WGA and Con A samples
6) Compare ratios from Alzheimer's patients to non-Alzheimer's patients

Saez-Valero et al. teach that there is a statistically significant difference in the amount of AChe unbound to WGA between control patients and those with Alzheimer's disease (see particularly p. 1602, Table 1, and p. 1602, first column, final paragraph). Saez-Valero et al. do not teach using labeled WGA. Sigma catalog pp. 1824 – 1825 indicates that WGA was available conjugated to labels (FITC product #L4895, TRITC L5266, biotin L5142, ferritin L1263, peroxidase L3892, L7017, L0390, Evans Blue L9884, 10nm colloidal gold L1894) and to sepharose (L6257). Sigma catalog (p. 1799) teaches that the reagent to which a lectin is conjugated does not alter the specificity of the lectin. It would have been obvious for one of ordinary skill in the art to use biotin-labled WGA in the method of Saez-Valero et al. with a reasonable expectation of success. A motivation for using a biotin based system in a lectin-detection method is provided by Savage et al. in the paragraph spanning pp. 130 – 131: this system has an increased sensitivity and does not alter the binding properties of the lectin.

It is noted that the method of Saez-Valero et al. includes a ratio-calculating step, which is not required for the claimed method. However, rejection under 35 U.S.C. 103(a) is proper because a) the teachings of Saez-Valero et al. indicate that there is a significant difference between AChe bound to WGA in Alzheimer's and control patients and b) the "comprising" claim language of claims 1 – 4 allows for the inclusion of other method steps. Furthermore, using a biotin-based method would be able to directly provide the necessary data, the amount of protein bound to the lectin, as opposed to unbound to the lectin as is generated by the method of Saez-Valero et al.

Claims 1 – 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Small et al. (WO 99/15695, reference AF on the information disclosure statement filed 26 August 2002) in view of Sigma catalog and Savage et al. Small et al. (p. 9, line 15 – p. 10, line 37) teach a method of diagnosing Alzheimer's disease by incubating protein isolated from CSF with WGA. Small et al. used WGA coupled to Sepharose and found that their lectin binding analysis was 80% sensitive and 97% specific in the diagnosis of Alzheimer's disease. Small et al. do not teach using biotin-labeled WGA. As explained above, Sigma catalog teaches that the molecule to which a lectin is coupled does not alter its binding properties, and Savage et al. teach that biotin-based lectin assays are advantageous in that they offer increased sensitivity. It would have been obvious to one of ordinary skill in the art to use biotin-coupled WGA in the assay of Small et al., with a reasonable expectation of success.

Claims 1 – 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeGasperi et al. (1990. Laboratory Investigation 63:385-393) in view of Savage et al. The claims are drawn to methods of diagnosing disorders associated with altered protein glycosylation (claim 1), wherein the body fluid is blood, CSF, or serum (claim 2), and wherein WGA is labeled with biotin (claim 3). DeGasperi et al. teach a method of detecting alterations in glycosylation patterns of proteins in tissue samples from patients with Gaucher disease. DeGasperi et al. teach that Gaucher disease is associated with alterations in protein glycosylation. DeGasperi et al. used biotin-labeled lectins, including WGA, to detect alterations in glycosylation patterns (see p. 386, first two complete paragraphs). DeGasperi et al. performed their method on whole blood (see Table 2), and compared the results to sample from control patients (p. 386, first sentence of first complete paragraph).

DeGasperi et al. do not teach isolating protein from the sample. Savage et al. (p. 138 – 139) teach a method of detecting glycoproteins with bionylated lectins, wherein the protein is

separated by electrophoresis and then blotted onto a solid matrix. Separation by electrophoresis is a standard technique, was used by the inventors in the instant specification, and entails prior purification of the protein from the tissue or fluid sample. It would have been obvious to one of ordinary skill in the art to use the electrophoretic technique of Savage et al. to diagnose Gaucher disease, with a reasonable expectation of success. A motivation for doing so would be to determine which proteins have altered glycosylation patterns in Gaucher disease, which is an advantage that blotting techniques provide over immunohistochemical techniques. Savage et al. teach that a particular glycoprotein can be detected by any one of several methods using biotinylated lectin, including both immunohistochemsitry and blotting (see p. 130).

Claims 1 – 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Szumanska et al. (reference AM on the information disclosure statement filed 26 August 2002) in view of Saez-Valero et al. Szumanska et al. teach a method of detecting changes in the WGA staining pattern in amyloid plaques, using biotin-labeled lectin. Szumanska et al. demonstrate that there is more intense staining in plaques from patients with Alzheimer's disease than in plaques from patients with Gersmann-Straussler syndrome, a disease caused by a virus that leads to plaques in the brain (see p. 2, Table 1), and that amyloid plaques in kidneys do not stain with WGA (see p. 8, legend for Fig. 23). Thus their method can be used for the diagnosis of Alzheimer's disease.

Szumanska et al. do not teach a method of detecting changes in biotin-labeled WGA staining pattern when a sample of protein extracted from a body fluid is provided. Saez-Valero et al. teach a method of diagnosing Alzheimer's disease using a protein sample extracted from CSF. It would have been obvious to one of ordinary skill in the art to use the method of Szumanska et al. on a sample of protein extracted from CSF, as described in Saez-Valero et al., with a reasonable expectation of success. A motivation for doing so is given by Saez-Valero et al. on p. 1600:

> Therefore, there is a need to identify specific biochemical markers of AD. So far, analysis of blood or CSF has not yielded a biochemical marker of sufficient diagnostic value, although detectable differences are reported in the levels of certain proteins.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 – 4 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,461,831, issued 8 October 2002, in view of Sigma catalog and Savage et al. The '831 patent is the patent that matured from the national stage application of WO99/15695, cited in the rejections under 35 U.S.C. § 103, above. Claim 1 of the '831 patent is drawn to a method of diagnosing Alzheimer's disease said method having the following steps:

1) providing a sample of an appropriate body fluid from a patient

2) isolating the protein by centrifugation

3) detecting the presence in said sample of an AChe with an altered glycosylation pattern such that it has a relatively lesser affinity for Con A and a greater affinity for WGA than an AChe with an unaltered glycosylation pattern

4) correlating the presence of said AChe with an altered glycosylation pattern with Alzheimer's disease.

Claims 1 – 4 of the instant application are drawn to methods of diagnosing Alzheimer's disease in a patient. The claims differ from claim 1 of the '831 patent in that they require the use of a labeled (claims 1, 2, and 4), or biotin-labeled (claim 3) WGA, which is not explicitly required by claim 1 of the '831 patent. The specification of the '831 patent (see, for example column 3, lines 2 – 6) discloses that lectins including WGA can be used to detect the altered glycosylation pattern. As detailed above, Sigma catalog teaches that the reagent to which a lectin is coupled does not alter its binding properties, and Savage et al. teach that using biotin is

advantageous because it increases the sensitivity of the assay. Although claim 1 of the '831 patent recites the relative binding affinities of AChe to Con A and WGA, it does not require both lectins to be used in the assay.

Claims 1 – 4 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 28 and 29 of copending Application No. 10/648,548. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application require the use of labeled WGA, which is not an explicit requirement of claim 28 of the '548 application. However, claim 28 does require determining the amount of a protein bound to WGA, which could be performed with biotin-labeled WGA. It is acknowledged that claims 28 and 29 of the '548 application require additional steps not required for the claims of the instant application. However, the instant claims are drawn to methods comprising the stated steps and therefore can include other irrelevant steps.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SHARON L. TURNER, PH.D.
PATENT EXAMINER

Daniel E. Kolker, Ph.D.
February 22, 2005

2-22-05